REMARKS

Claims 3, 4, 7, 8, and 10-13 are currently pending in the application. Only claim 3 is in independent form.

Applicants wish to express their appreciation for the courtesies extended Applicants' representive, Amy E. Rinaldo, during a telephonic interview conducted in February 2003.

Claims 5 and 9 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention. As these claims have been cancelled in order to further prosecution, the present rejection is rendered moot and reconsideration of the rejection is respectfully requested.

Claims 3-4, 7-9, 10 and 13-16 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Office Action states that while the specification is enabling for inhibiting the expression of tumor necrosis factor-alpha (TNF-α) *in vitro*, it does not reasonably provide enablement for modulating, which includes enhancing and inhibiting, the expression of TNF-α *in vivo*. In order to further prosecution, the claims have previously been amended to specifically recite that the antisense is only inhibiting the expression of TNF-α, thus overcoming a portion of the present rejection.

The Office Action also states that the specification as filed does not disclose a successful *in vivo* delivery of the antisense/ribozyme compounds and that such knowledge is not currently known in the art. The Office Action states that the current state of the art teaches that the behavior of antisense oligonucleotides *in vivo* and *in vitro*

is unpredictable. However, as set forth in the previously attached paper written by Applicants, there is disclosed that the *in vivo* use of the method as set forth in the present application does perform as indicated in the *in vitro* studies. Specifically, the previously attached article shows data collected by the Applicants utilizing the methods of the present invention in rats. This study shows that rats treated with the methods and compositions of the present application developed the results that were predicted based upon the *in vitro* study. Further, the currently attached Figure clearly shows that the intra-carotid delivery of ORF-4 one hour after intracerebral hemorrhage shows a dose dependent inhibition of TNF-α expression in brain. TNF-α was measured by real time RT-PCR using RNA extracted from brain following intracerebral hemorrhage. This Figure shows that 2mg of antisense molecule significantly reduced TNF-α expression *in vivo* in brain. This will lead to improved neurobehavorial outcomes and shows a potent anti-inflammatory effect when delivered intra-arterially through the corotid artery, ipsolateral to the side of the lesion. The vector used is identical to the vector disclosed in the application as filed. Further, as stated at page 19 of the application, the vector can be administered to the circulatory system. Accordingly, there is sufficient support for the specification as currently pending, and reconsideration of the rejection is respectfully requested.

Claim 5 stands rejected under 35 U.S.C. § 102(e) as being anticipated by the Nyce, et al patent, the Taylor, et al. patent, the Sioud, et al. patent, and the Hartman, et al. patent. As claims 5 and 9 have been canceled without prejudice, the present rejections are rendered moot and reconsideration of the rejection are respectfully requested.

In view of the present amendment and foregoing remarks, reconsideration of the rejections and advancement of the case to issue are respectfully requested.

The Commissioner is authorized to charge any fee or credit any overpayment in connection with this communication to our Deposit Account No. 11-1449.

Respectfully submitted,

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Dated: March 5, 2003

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I hereby certify that this correspondence is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231 on March 5, 2003.

Angel Webb

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION

Page 1, line 9-11:

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims priority from United States Provisional Application 60/062,718. This application is a continuation application of U[.]nited S[.]tates Patent Application Serial No. 0[8]9/176,862, filed October 22, 1998.

IN THE CLAIMS:

Please cancel claims 5, 6, and 9.